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(54) Inhibition of metabolic oxalate formation

(57) It has been found that administration of a sulfhydryl compound (in particular, cysteine) or a cysteine derivative is effective in treating or preventing diseases resulting from defects of oxalate excretion (e.g. renal stones or gout). The sulfhydryl compound or cysteine derivative is administered either by itself or in the form of a pharmaceutical or veterinary composition.

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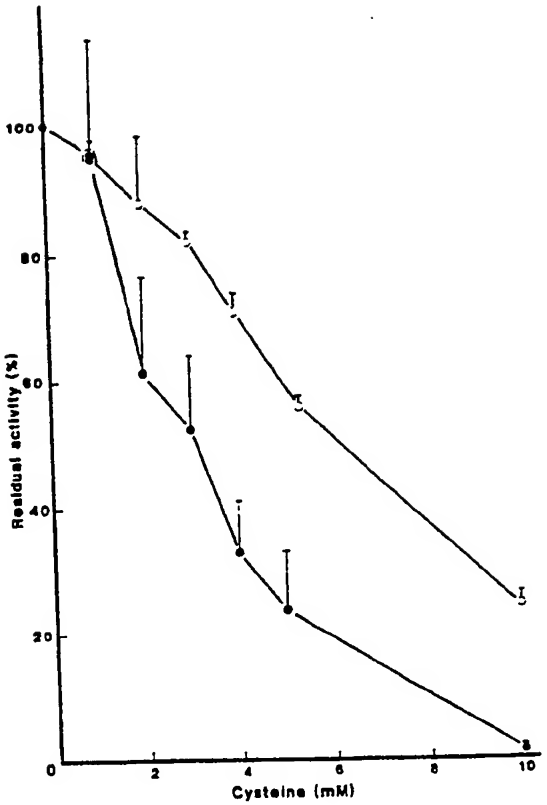


FIGURE 1

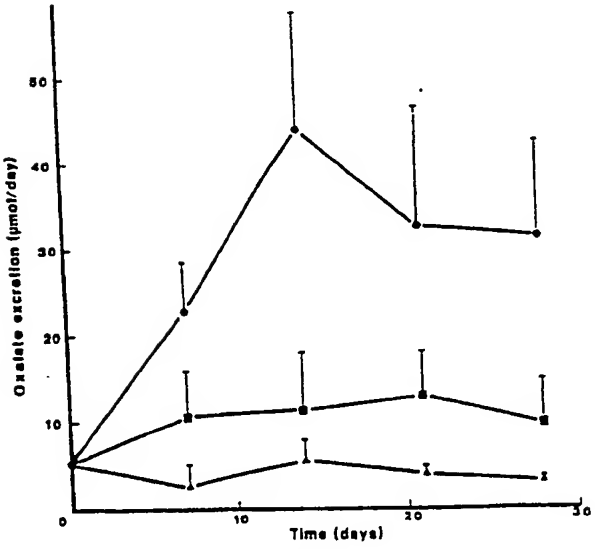
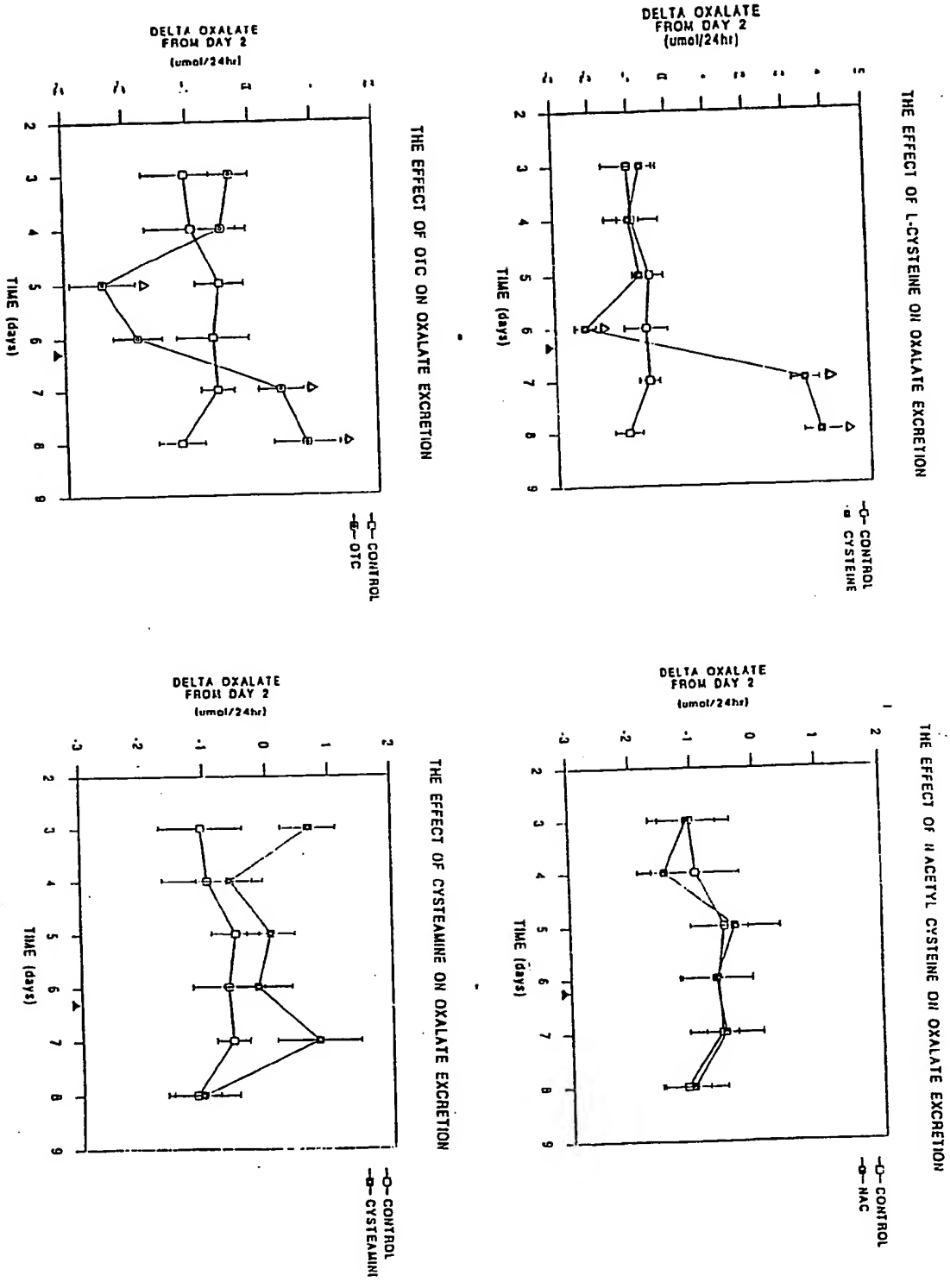


FIGURE 2

FIGURE 3



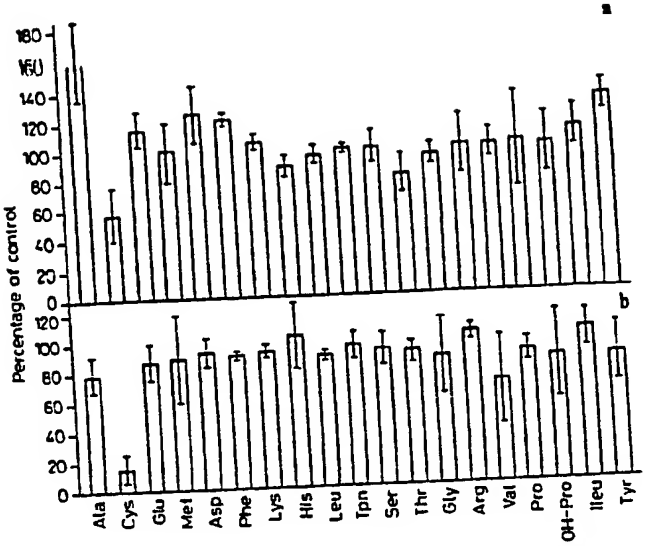


FIGURE 4

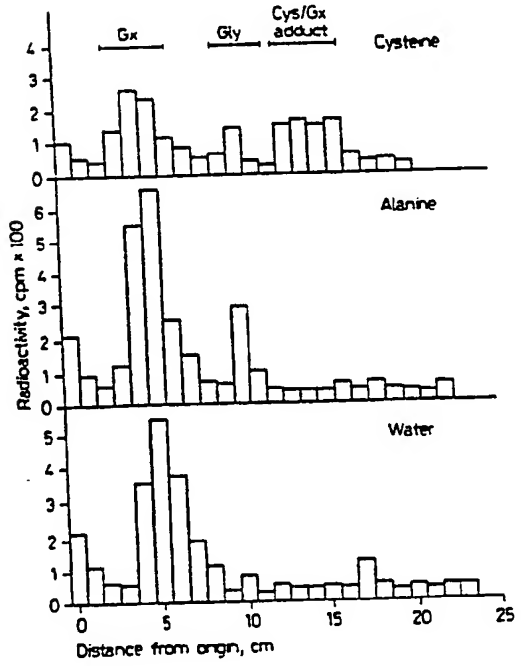


FIGURE 5

INHIBITION OF METABOLIC OXALATE FORMATION

This invention relates to the treatment of disorders resulting from elevated levels of endogenous oxalate formation, and in particular concerns the treatment of renal stones and gout.

BACKGROUND OF THE INVENTION

Calcium oxalate, along with varying proportions of calcium phosphate, is the major component in 70% of all renal stones in affluent countries (1-3). For many years, urinary oxalate was considered to come largely from the oxalate which is naturally present in foodstuffs and absorbed from the gut (1). However, with the possible exception of patients with disease-related and/or surgically induced short-bowel syndromes, only 2-8% of the 1.0-1.5 mmoles of oxalate ingested daily is absorbed by the intestine. If all this absorbed oxalate is excreted in the urine, it only accounts for 10-15% of the daily urinary oxalate output of 0.16-0.56 mmol per day in humans (4). Although there is still some controversy as to the exact contribution of endogenous production to the total urinary oxalate excretion, there is no doubt that endogenous oxalate production is one of the factors contributing to the hyperoxaluria seen in many patients with iodiopathic calcium oxalate stones (5). Accordingly, if the endogenous production of oxalate can be controlled, calcium oxalate stone formation can be inhibited or prevented.

Our studies have shown that oxalate production, from a variety of dietary sources, can be controlled via the common pathway in which glycolate and glyoxylate (the immediate precursors of oxalate) are metabolised. The reactions involved are common to all the proposed routes of oxalate formation and the control of these reactions would appear to be important in the regulation of oxalate formation. It has been suggested that inhibition of one or more of the enzymes catalyzing these reactions may have a therapeutic role in reducing renal stone disease (6). However, our work has indicated that doubt remains as to whether inhibiting these key enzymes can be considered as a realistic mechanism to prevent oxalate formation (7). In another endeavour to limit

endogenous oxalate production, we have studied the reactions that divert glyoxylate from oxalate production. Glyoxylate is a highly reactive compound that is able to participate in many reactions in mammalian tissues (1). Of the reactions that divert glyoxylate from oxalate production, the two most important are decarboxylation and transamination. Decarboxylation of glyoxylate is catalyzed by 2-oxoglutarate:glyoxylate carboligase, in which 2-oxoglutarate and glyoxylate are synergistically decarboxylated. The reaction occurs in the mitochondria and is associated with the multienzyme complex, 2-oxoglutarate dehydrogenase. Glyoxylate transamination to glycine is catalyzed by a number of peroxisomal enzymes, with many amino acids acting as the amino donor. Transamination by alanine-glyoxylate aminotransferase (EC 2.6.1.44) is the most important of these reactions, and a deficiency of this enzyme in human liver has been shown to be the underlying cause of primary hyperoxaluria (8). Using isolated rat hepatocytes, it has now been found that, compared with the alanine-glyoxylate transamination, most of the other transamination reactions did not have a significant effect on oxalate formation from glyoxylate, with the exception of certain sulfhydryl compounds (in particular, cysteine) and cysteine derivatives, which caused a substantial reduction in oxalate formation. A particularly effective compound was cysteine. Investigation of the reaction products of cysteine with glyoxylate, using paper chromatography, showed that, besides the normal transamination product, glycine, another stable product was formed. It was postulated that this product could be a glyoxylate-cysteine adduct, which prevented glyoxylate from being further oxidized to oxalate.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a pharmaceutical or veterinary composition, for the treatment or prevention of diseases resulting from defects of oxalate excretion, comprising a sulfhydryl compound (in particular, cysteine) or a cysteine derivative, in a pharmaceutically acceptable vehicle.

According to a further aspect of this invention, there is provided a method of treatment or prevention of diseases resulting from defects of oxalate excretion, comprising the administration of a sulfhydryl compound (in particular, cysteine) or a cysteine derivative, either by itself or in the form of a pharmaceutical or veterinary composition (as described above).

The compounds used in the present invention are sulfhydryl compounds such as cysteine, dithiothreitol and glutathione; cysteine-releasing agents such as N-acetyl-cysteine, cysteinyl-glycine and 2-oxothiazolidine-4-carboxylate; and other cysteine derivatives such as cysteamine and penicillamine. Preferred compounds are cysteine (in particular), cysteamine and 2-oxothiazolidine-4-carboxylate. Where applicable, both D- and L- isomers are to be included within the scope of the invention (e.g. D- and L-cysteine, and derivatives thereof).

The sulfhydryl compound or cysteine derivative inhibits endogenous oxalate formation, and is, therefore, effective in the treatment or prevention of such disorders as renal stones and gout.

PHARMACOLOGICAL TESTING

MATERIALS AND METHODS

Materials. [1-^{14}C]-glyoxylate was purchased from Amersham, Sydney, NSW, Australia. Cysteine and 2-mercaptoethanol were from the Sigma Chemical Co., Mo., USA, N-acetyl cysteine, dithiothreitol and glutathione were from Boehringer-Mannheim, North Ryde, NSW, Australia, and thioglycolate was from Ajax Chemicals, Adelaide, SA, Australia. Captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline) is an antihypertensive agent from E R Squibb and Sons Pty Ltd, Melbourne, VIC, Australia. The sources of all other chemicals and reagents have been described previously (7, 9, 10).

Methods. The preparation of rat liver homogenates (10) and hepatocytes (7) have been described previously.

For the preparation of the rat liver homogenates, the liver was rinsed in ice-cold saline to remove blood, cut into

thin slices and placed in two volumes of ice-cold 10 mmol/l sodium phosphate buffer, pH 7.4, containing 0.15 mol/l KCl and 0.8 mmol/l $MgCl_2$. The homogenate was then prepared with one stroke of a Teflon pestle in a Potter-Elvehjem homogeniser and strained through one layer of muslin. Isolated hepatocytes were prepared from fed male Porton rats (250-350 gm) by collagenase perfusion of the livers. The cells were diluted in 10 mmol/l sodium phosphate buffer, pH 7.4, containing 140 mmol/l sodium chloride, 5.4 mmol/l KCl and one mmol/l $MgSO_4$ and through which 100% O_2 had been bubbled for 10 min. Cell viability was 85-95%, as assessed by Trypan Blue exclusion. Cells were assayed at a concentration of 10^7 cells/ml. In studies with homogenates and hepatocytes, reactions were performed in glass scintillation vials which were flushed with oxygen, capped and incubated for 30 min at 37°C in a reciprocating shaking water bath. In these reactions, both the glyoxylate and the sulfhydryl reagents were tested at a concentration of five mmol/l. At the completion of the incubation, the $^{14}CO_2$ produced from [1-^{14}C]-glyoxylate was collected into Hyamine hydroxide by incubation for 2 hours and then the incubation vial assayed for ^{14}C-oxalate by adding 0.1 ml of 0.4 mol/l citric acid, pH 4.5, containing 0.4 units of oxalate decarboxylase (EC 4.1.1.2) per ml, and determining the $^{14}CO_2$ liberated. Urinary oxalate was measured using an immobilized oxalate oxidase method and plasma biochemical analyses determined using a Technicon SMAC II.

For the *in vivo* studies, rats were housed in cages in groups of four or five. Ad libitum food and fluid intake were measured daily, as were the body weights of each rat. For 24 hours urine collection, the rats were placed into individual metabolic cages and the urine collected into 0.5 ml of 5 mol/l HCl.

Rats were made hyperoxaluric by administering either 0.25% (v/v) or 0.75% (v/v) ethylene glycol in their drinking water (11, 12). The cysteine-treated rats were given daily intraperitoneal injections of 2 ml of 10% (w/v) cysteine in physiological saline. The non-treated group were injected

with 2 ml of saline.

RESULTS

I. *Effect of sulfhydryl compounds on CO_2 and oxalate production.* The effect of sulfhydryl compounds on CO_2 and oxalate production from glyoxylate by homogenates and hepatocytes is shown in Table 1 below. All the compounds tested had some inhibitory effect on CO_2 formation by homogenates, with the greatest inhibition occurring with the addition of cysteine. In the studies of CO_2 formation by hepatocytes, only cysteine and N-acetyl cysteine caused any significant inhibition.

The sulfhydryl compounds, dithiothreitol, 2-mercaptoethanol, glutathione and captopril, inhibited oxalate formation by homogenates to varying degrees, but cysteine caused a greater than 50% inhibition. With hepatocytes, all the cysteine-type compounds inhibited oxalate production, whereas glutathione had no effect. The most significant inhibitor was cysteine, which produced almost total inhibition of oxalate production. None of these compounds had any effect, over the incubation period, on the viability of the hepatocytes as determined by Trypan Blue exclusion.

Table 1. Effect of sulfhydryl compounds on CO_2 production and oxalate formation.

	Homogenate		Hepatocytes	
Compound	CO_2	Oxalate	CO_2	Oxalate
	(% residual activity)			
cysteine	19.7 ± 8.0*	47.3 ± 15.8*	11.7 ± 6.5*	7.3 ± 10.4*
N-acetyl cysteine	76.0 ± 17.1	101.3 ± 6.9	27.0 ± 9.3*	69.5 ± 5.5
dithiothreitol	53.0 ± 5.4*	74.7 ± 13.8	99.7 ± 23.0	55.0 ± 17.9
glutathione	88.3 ± 9.1	103.7 ± 6.0	93.0 ± 9.1	99.7 ± 17.2
thioglycolate	69.0 ± 11.3	94.7 ± 11.1	91.3 ± 13.8	44.0 ± 9.9*
2-mercaptoethanol	57.0 ± 4.1*	64.7 ± 7.3*	112.7 ± 21.5	67.0 ± 25.7
captopril	59.7 ± 9.9*	81.3 ± 4.0	86.7 ± 17.5	65.3 ± 9.0

Results (mean ± SD) are shown relative to the control with no addition, and are from 3 different homogenate and hepatocyte preparations which were assayed in duplicate.

The control CO_2 production was 0.043 μmol/min/gm wet weight by homogenates and 0.015 μmol/min/10^7 cells in hepatocytes, and the oxalate production 0.025μmol/min/gm wet weight by homogenates and 0.016 μmol/min/10^7 cells in hepatocytes.

Significantly different from the controls: $^{*}p<0.05$, $^{+}p<0.01$.

II. *Effect of cysteine concentration in vitro.* Since the most consistent and greatest inhibition of oxalate production by these sulfhydryl compounds was achieved with cysteine, the effect of varying cysteine concentration on CO_2 production and oxalate formation by hepatocytes was investigated (Figure 1). As the cysteine concentration is increased, there is a decrease in both the CO_2 formation and oxalate production. The viability of the hepatocytes, as measured by Trypan Blue exclusion, was not affected by these cysteine concentrations.

III. *Effect of cysteine in vivo.* Hyperoxaluria was induced in rats by administering 0.25% or 0.75% ethylene glycol in their drinking water (13, 14). Initially, cysteine was also included in the water but it was found that the rats disliked the taste, and thus the cysteine was administered by daily intraperitoneal injection. A control group, which received no ethylene glycol, was injected with cysteine only. There was no statistically significant difference in the food intakes, body weights and ethylene glycol intake between the groups given saline and the cysteine-treated group (determined by analysis of variance). The rats did increase their body weight over the duration of the experiment, but the increase was the same for all the groups. At autopsy, there was no difference in the size or appearance of the kidneys and livers of the various groups. In addition, on dissection, the kidneys appeared macroscopically normal and no stones were detected. In contrast, when the concentration

of ethylene glycol is increased to 1%, there is a significant increase in the deposition of visible crystals (12). Biochemical analyses of the plasma collected at the conclusion of the treatments showed no significant changes in electrolytes, creatinine, glucose, uric acid, calcium or phosphate in any of the three groups.

The major difference between groups was the effect of cysteine administration on the oxalate excretion of the ethylene glycol-treated animals. Only the results for the 0.75% ethylene glycol treated rats are shown in Figure 2. The results with 0.25% ethylene glycol treated rats were similar, except that the level of urinary oxalate excretion was about half that of the 0.75% ethylene glycol treated rats. In both cases, there is a dramatic reduction in the oxalate excretion due to the cysteine treatment in ethylene glycol-treated rats. This decrease in the oxalate excretion occurs rapidly and was maintained throughout the duration of the experiments.

Similar results were obtained with rats rendered hyperoxaluric by injection of either glycolate or glyoxylate. They were then also injected with either saline or cysteine and the urinary oxalate excretion measured. Intraperitoneal injection of cysteine was required because the rats did not tolerate cysteine in their drinking water. Treating the rats with glycolate or glyoxylate causes a greater than 3-fold increase in the urinary excretion of oxalate. However, in the presence of cysteine the urinary excretion of oxalate is decreased 3- to 4-fold in all the three groups (Table 2).

Table 2. The effects of cysteine on oxalate formation in vivo

Substrate	Cysteine	Oxalate µM/day	Inhibition %
No addition	-	6.8 ± 4.5	
	+	2.9 ± 0.5*	57.6
Glycolate	-	25.8 ± 7.3	
	+	9.9 ± 1.6*	61.7
Glyoxylate	-	22.2 ± 2.3	
	+	5.4 ± 3.0*	75.7

Oxalate results are given as mean ± SD (n = 8). *$p<0.001$.

Oral administration

A consistent decrease in normal oxalate excretion was seen when the rats were first put into metabolic cages, as they adjusted to their new surroundings and the meal feeding regimen. This decrease occurred during the first 2 days, after which oxalate excretion plateaued. Therefore, changes in urinary oxalate as a result of sulfhydryl administration are taken from day 2, due to variability of the rats during the initial adjustment period. Results are shown in Figure 3.

Only oral doses of L-oxothiazolidine-4-carboxylate (L-OTC) and L-cysteine had any significant effect on oxalate excretion in rats on normal diets. During the first 2 days of being on the L-OTC supplemented diet, the rats showed no significant change in urinary oxalate. On the 3rd day of L-OTC treatment (Day 5), urinary oxalate excretion significantly decreased, an effect that was also seen on the last day of OTC treatment. When the rats were returned to a normal diet on day 7 of the experiment, the 24hr excretion of

oxalate increased, and by day 8 was significantly greater than the controls.

The results with L-cysteine treated rats were similar to L-OTC. The first 3 days of L-cysteine treatment did not affect the rats' oxalate excretion, but on the 4th day of treatment (Day 6) urinary oxalate was decreased by 2.22μmol/24hr. Again when these rats were taken off the cysteine supplement, a rebound effect was seen, with the urinary oxalate excretion increasing to levels significantly above that of the control group.

Cysteamine and N-acetylcysteine had no significant effect on 24hr urinary oxalate.

These studies, and other studies in chicks, have shown that L-OTC is a palatable and stable precursor of cysteine, which is utilized effectively, regardless of the route of administration.

IV. *Transamination Studies*

Glyoxylate transamination was measured radiochemically by the formation of [^{14}C]-glycine from [1-^{14}C]-glyoxylate (15). After incubation, excess hydrogen peroxide is added to oxidise the [1-^{14}C]-glyoxylate to $^{14}CO_2$, followed by the addition of perchloric acid to remove the $^{14}CO_2$. The amount of acid-stable product is a measure of the transamination.

Paper Chromatography

The products of the transamination reaction were examined by paper chromatography. After incubation, the reaction was stopped by the addition of perchloric acid and then centrifuged at 5,000 g for 5 min. 30 μl of the supernatant was spotted onto Whatman No. 4 chromatography paper and the chromatogram developed using water-saturated phenol as the solvent. After running for 9 h, the paper was air-dried and then sprayed with ninhydrin (0.25% in acetone) to locate the amino acids. With this system, the R_f values were glycine, 0.54; alanine, 0.68; cysteine, 0.43 and glutamate, 0.41. In addition, the chromatogram was cut into 1 cm strips and the radioactivity determined.

Transamination Reactions with Glyoxylate

Glyoxylate transamination with a variety of amino acids

was measured in homogenates by determining the acid-stable products after stopping the reaction with hydrogen peroxide. The results in Table 3 are shown relative to alanine, which is the most active amino acid in this transamination reaction.

Table 3. Rat liver homogenate transamination reactions with glyoxylate

Amino acid	Relative activity	Amino acid	Relative activity
Alanine	100	Serine	15.0 ± 8.2
Glutamic acid	53.1 ± 14.3	Tryptophan	3.2 ± 2.4
Methionine	38.9 ± 6.2	Isoleucine	5.9 ± 3.6
Phenylalanine	35.5 ± 10.8	Valine	2.6 ± 0.4
Glutamine	49.0 ± 12.5	Hydroxyproline	3.4 ± 2.2
Histidine	21.1 ± 12.2	Proline	0.6 ± 1.0
Leucine	26.3 ± 8.9	Threonine	5.0 ± 2.0
Asparagine	33.6 ± 6.9	Tyrosine	9.0 ± 8.2
Aspartic acid	11.2 ± 3.7	Glycine	2.3 ± 1.9
Arginine	6.7 ± 3.0	Cysteine	93.0 ± 7.1
Lysine	3.0 ± 4.0		

The results (mean ±SD:n = 4) are relative to alanine:glyoxylate transamination.

Several of the amino acids tested formed acid-stable products, but the most significant and unexpected reaction was that with cysteine, which appeared to be as active as alanine.

The effect of transamination on CO_2 and oxalate production from glyoxylate was studied in hepatocytes by incubating 1 m*M* glyoxylate in the presence of 20 m*M* amino

acid. The CO_2 and oxalate results are shown in Fig. 4 relative to the control with no added amino acid. The CO_2 production varied between 80 and 120% of the control, with the exception of alanine which increased CO_2 production to 160% of the control and cysteine which reduced it by about 25%. In addition, while most amino acids had little effect on oxalate production, cysteine caused an 80% inhibition.

To further investigate this inhibitory effect of cysteine, the products of the transamination reaction between glyoxylate and cysteine were examined. After incubation of hepatocytes with the reactants, the products were separated by paper chromatography. The chromatogram was sprayed with ninhydrin to determine the position of the amino acids, and, concomitantly, the location of the radioactivity was determined. The results (Fig. 5) show that in all three reactions, there is an unreacted radioactive glyoxylate spot. In addition, with alanine and cysteine, there were counts which corresponded to the glycine spot, which is the expected product of the reaction. However, in the presence of cysteine, there is an extra radioactive spot which is unique to cysteine and not found with any other amino acid.

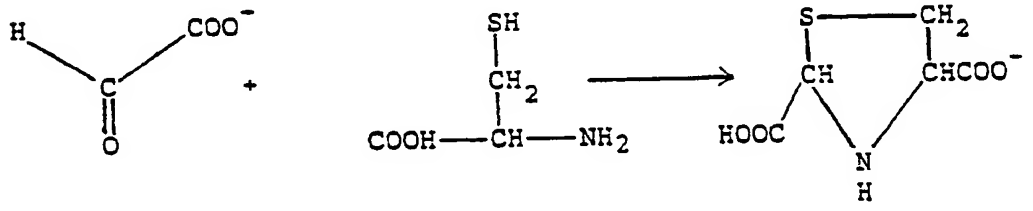
DISCUSSION AND CONCLUSIONS

Cysteine and a number of derivatives thereof have been shown to inhibit CO_2 and oxalate formation by rat liver homogenates and hepatocytes. Possibly, these compounds inhibit the key regulatory enzymes, glycolate oxidase and glycolate dehydrogenase. The most significant inhibition occurs with cysteine, and this is concentration-dependent. At high enough concentrations, cysteine will prevent oxalate formation completely in hepatocytes (Fig. 1).

Hyperoxaluria is one of the major risk factors for the formation of urinary calcium oxalate stones (16) and minor changes in urinary oxalate concentration are a more important determinant of urinary calcium oxalate supersaturation than is urinary calcium. Although the use of rats given ethylene glycol as a model for hyperoxaluria has been questioned at times, it is still considered to be the most appropriate model (11, 12). At the concentrations of ethylene glycol that

were used (0.25% and 0.75%), there were no significant changes in the appearance and size of the kidneys and the livers of any of the treated groups compared to the non-treated groups.

Cysteine treatment of hyperoxaluric rats caused a rapid and marked decrease in urinary oxalate excretion, which was maintained over the duration of treatment (28 days). Over this time period, the level of urinary oxalate excretion in these ethylene-treated rats approached that of the controls. We have also been able to show that rats injected with glycolate and glyoxylate had reduced oxalate excretion when injected with cysteine. Investigation of the products of the transamination reaction between cysteine and glyoxylate indicated that another compound besides glycine was formed. Although we do not wish to be bound by preliminary speculations, it is probable that this other compound is the cysteine-glyoxylate adduct which has been described previously (13, 14).



glyoxylate cysteine adduct 2-carboxy-4-thiazolidine carboxylate

It is possible that the reduction in oxalate production was due to the formation of the adduct preventing glyoxylate being further metabolised to oxalate. The present results are also consistent with that explanation, because the metabolism of ethylene glycol to oxalate is via glyoxylate which would allow the adduct to be formed (17). Further evidence for adduct formation is that the reduction in the CO_2 formation suggests that the normal metabolism of ethylene glycol has been prevented from occurring. The importance of these observations is that they demonstrate that it is possible to

limit metabolic oxalate production, and indicate that cysteine and other similar compounds have potential as therapeutic agents in the prevention of renal stones.

Glyoxylate forms adducts with a number of nucleophiles, including thiols, primary amines and alcohols (14). The initial adduct formed on the addition of any nucleophile to glyoxylate is an -hydroxy acid, but many of these can then react further to form other compounds (including stable cyclic structures). At neutral pH and 37°C, the time required to form these adducts is in the order of seconds or less to minutes. The formation is favoured for thiols approximately an order of magnitude greater than for amines and three orders of magnitude greater than for alcohols. In his work on glyoxylate adducts, Hamilton suggested that they are the true physiological substrates for various peroxisomal oxidases such as D-amino acid oxidase, D-aspartate oxidase and L-hydroxy acid oxidase and that the enzymic products will ultimately hydrolyse to form oxalate (14). However, the enzymic products are stable to nonenzymatic hydrolysis under physiological conditions for many days, and the enzymes required to catalyze such reactions have not been found. Thus, it appears that these products will be excreted before any significant hydrolysis can take place, thus preventing the accumulation of oxalate. The variability of the results with the sulfhydryl reagents reported here may be a measure of the extent of adduct formation, resulting in different amounts of glyoxylate being available for further metabolism.

The above results suggest that cysteine and other similar compounds act as urinary oxalate lowering agents by preventing glyoxylate oxidation to oxalate. In our rat experiments, there did not appear to be any side-effects due to the formation of the glyoxylate-cysteine adduct.

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DESCRIPTION OF DRAWINGS

Fig. 1 The effect of varying cysteine concentration on CO_2 and oxalate formation by hepatocytes. Isolated hepatocytes were incubated with varying concentrations of cysteine and the $^{14}CO_2$ liberated (●) and [^{14}C]-oxalate formed (o) from 5 mmol/l [1-14C]-glyoxylate determined as described in the text. The results are shown as mean ± SD (n=3).

Fig. 2 The urinary oxalate excretion from rats treated with cysteine (▲), ethylene glycol (●) and ethylene glycol plus cysteine (■). Details of the experimental design are given in the text. Results are shown as mean ± SD ($n \geq 4$).

Fig. 3 The effect of various orally administered sulfhydryl compounds on oxalate excretion. The results shown are mean = SEM (n=6). ▲ = $p < 0.05$.

Fig. 4 The effects of 5 m*M* amino acids on the formation of CO_2 (a) and oxalate (b) formation from [1-14C]-glyoxylate by isolated rat hepatocytes. The results are shown relative to the control without the added amino acid as expressed as mean ± SD (n=3).

Fig. 5 Paper chromatography of the radioactive products of the glyoxylate transamination reaction catalysed by hepatocytes. 30 ul of reaction products were spotted at the origin and the chromatogram developed as described in the text. After drying, the chromatogram was cut into 1 cm strips and the radioactivity determined.

CLAIMS

1. A pharmaceutical or veterinary composition, for the treatment or prevention of diseases resulting from defects of oxalate excretion, comprising, as active ingredient, a sulfhydryl compound or a cysteine derivative, in a pharmaceutically acceptable vehicle.

2. A pharmaceutical or veterinary composition according to claim 1 comprising, as active ingredient, cysteine, dithiothreitol, glutathione, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

3. A pharmaceutical or veterinary composition according to claim 1 or claim 2 comprising, as active ingredient, cysteine, cysteamine or 2-oxothiazolidine-4-carboxylate.

4. A pharmaceutical or veterinary composition, for the treatment or prevention of renal stones or gout, comprising, as active ingredient, a sulfhydryl compound or a cysteine derivative, in a pharmaceutically acceptable vehicle.

5. A pharmaceutical or veterinary composition according to claim 4 comprising, as active ingredient, cysteine, dithiothreitol, glutathione, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

6. A pharmaceutical or veterinary composition according to claim 4 or claim 5 comprising, as active ingredient, cysteine, cysteamine or 2-oxothiazolidine-4-carboxylate.

7. A method of treating or preventing a disease resulting from a defect of oxalate excretion comprising administration of a sulfhydryl compound or a cysteine derivative.

8. A method according to claim 7, wherein the sulfhydryl compound or cysteine derivative is cysteine, dithiothreitol, glutathione, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

9. A method according to claim 7 or claim 8, wherein the sulfhydryl compound or cysteine derivative is cysteine, cysteamine or 2-oxothiazolidine-4-carboxylate.

10. A method of treating or preventing renal stones or gout comprising administration of a sulfhydryl compound or a cysteine derivative.

11. A method according to claim 10 comprising administration of cysteine, dithiothreitol, glutathione, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

12. A method according to claim 10 or claim 11 comprising administration of cysteine, cysteamine or 2-oxothiazolidine-4-carboxylate.

13. A pharmaceutical or veterinary composition according to any one of claims 1 to 6, substantially as described herein.

14. A method according to any one of claims 7 to 12, substantially as described herein.

15. The use of a sulfhydryl compound or a cysteine derivative for the manufacture of a medicament for a therapeutic and/or prophylatic treatment of a disease resulting from a defect of oxalate excretion.

16. The use as claimed in claim 7, wherein the sulfhydryl compound or cysteine derivative is cysteine, dithiothreitol, glutathione, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

17. The use as claimed in claim 15 or claim 16 wherein the sulfhydryl compound or cysteine derivative is cysteine, cysteamine or 2-oxothiazolidine-4-carboxylate.

18. The use of a sulfhydryl compound or a cysteine derivative for the manufacture of a medicament for the therapeutic and/or prophylatic treatment of renal stones or gout.

19. The use as claimed in claim 18 wherein the cysteine derivative is dithiothreitol, glutathioine, N-acetyl-cysteine, cysteinyl-glycine, 2-oxothiazolidine-4-carboxylate, cysteamine or penicillamine.

20. The use as claimed in claim 18 or claim 19 wherein the cysteine derivative is cysteamine or 2-oxothiazolidine-4-carboxylate.

21. A pharmaceutical or veterinary composition, for the treatment or prevention of diseases resulting from defects of oxalate excretion, substantially as hereinbefore described with reference to the accompanying drawings.

22. A method of treating or preventing a disease resulting from a defect of oxalate excretion, substantially as hereinbefore described.

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